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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,653	02/17/2005	Zhan-qi Niu	UNI-05-1016	8338

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EXAMINER

HENRY, MICHAEL C

ART UNIT	PAPER NUMBER
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1623

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/524,653	Applicant(s) NIU ET AL.	
	Examiner MICHAEL C. HENRY	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 January 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>09/24/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The following office action is a responsive to the Amendment filed, 01/28/08.

The amendment filed 01/28/08 affects the application, 10/524,653 as follows:

The responsive to applicants' arguments is contained herein below.

Claims 1-16 are pending in the application

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-5, 12-14, 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (Yao Xue Xue Bao = Acta Pharmaceuticals Sinica, (2001 May) vol. 36, No. 5, pages 329-333) in view of Habon et al. (Pharmazie (1984), 39 (12), pages 830-4).

In claim 1, applicant claims an inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivatives, comprising butylphthalide and cyclodextrin or cyclodextrin derivative, wherein the molar ratio of butylphthalide to cyclodextrin or cyclodextrin derivatives is 1:1-10.

Claims 2-5 are drawn to said inclusion complex involving the use of specific types of cyclodextrins. Claims 12-14 are drawn to a pharmaceutical composition comprising said complex and specific forms of said composition.

Xu et al. disclose butylphthalide which has antithrombotic activity and antiplatelet activity when administered to rats (see abstract).

The difference between applicant's claimed compound or composition and the compound or composition of Xu et al. is that applicant's compound is complexed with cyclodextrin.

Habon et al. disclose that complexation of drugs with cyclodextrin enhances the bioavailability of drugs in vivo (see abstract). Furthermore, Habon et al. disclose that the enhanced bioavailability of drugs upon complexation are due factors such as enhanced dissolution rates and higher solubility (see abstract). In addition, Habon et al. disclose that the enhanced bioavailability is controlled or depends on factors such as solubilities, stability constants and the molar ratio of drug to cyclodextrin. Habon et al. disclose that the compounds can be administered in oral dosage forms (see abstract).

It would have been obvious to one having ordinary skill in the art at the time the claimed invention was made in view of Xu et al. and Habon et al. to have prepared a complex of butylphthalide with cyclodextrin or a derivative in order to enhance the bioavailability of the drug due to complexation by administering said complex to a subject and consequently to improve the treatment of thrombosis.

One having ordinary skill in the art would have been motivated in view of Xu et al. and Habon et al. to have prepared a complex of butylphthalide with cyclodextrin or a derivative in order to enhance the bioavailability of the drug due to complexation by administering said complex to a subject and consequently to improve the treatment of thrombosis, based on factors such as the severity of the thrombosis and the type of subject treated. It should be noted that the use of specific ratios of drug to cyclodextrins also depends on factors such as the severity of the thrombosis and the type of subject treated. It should be noted that the use of specific forms or

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formulations of said drugs such as butylphthalide is well-known in the art and is well within the purview of a skilled artisan.

In claim 16, applicant claims a method of treating thrombosis comprising administering a therapeutically effective amount of the inclusion complex according to claim 1 to a patient.

Xu et al. disclose a method of treating thrombosis by administering butylphthalide having antithrombotic activity and antiplatelet activity to rats (see abstract).

The difference between applicant's claimed method and the method of Xu et al. is that applicant's compound is complexed with cyclodextrin.

Habon et al. disclose that complexation of drugs with cyclodextrin enhances the bioavailability of drugs in vivo (see abstract). Furthermore, Habon et al. disclose that the enhanced bioavailability of drugs upon complexation are due factors such as enhanced dissolution rates and higher solubility (see abstract). In addition, Habon et al. disclose that the enhanced bioavailability is controlled or depends on factors such as solubilities, stability constants and the molar ratio of drug to cyclodextrin. Habon et al. disclose that the compounds can be administered in oral dosage forms (see abstract).

It would have been obvious to one having ordinary skill in the art at the time the claimed invention was made in view of Xu et al. and Habon et al. to use the method of Xu et al. to treat thrombosis in a subject by administering a complex of butylphthalide with cyclodextrin or a derivative to said subject in order to enhance the bioavailability of the drug due to complexation and consequently to improve the treatment of thrombosis.

One having ordinary skill in the art would have been motivated in view of Xu et al. and Habon et al. to use the method of Xu et al. to treat thrombosis in a subject by administering a

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complex of butylphthalide with cyclodextrin or a derivative to said subject in order to enhance the bioavailability of the drug due to complexation and consequently to improve the treatment of thrombosis, based on factors such as the severity of the thrombosis and the type of subject treated. It should be noted that the use of specific ratios of drug to cyclodextrins also depends on factors such as the severity of the thrombosis and the type of subject treated.

Claims 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Habon et al. (Pharmazie (1984), 39 (12), pages 830-4) in view of Xu et al. (Yao Xue Xue Bao = Acta Pharmaceuticals Sinica, (2001 May) vol. 36, No. 5, pages 329-333).

In claim 6, applicant claims a process for preparing the inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivatives, comprising the steps of adding cyclodextrin or cyclodextrin derivatives into a suitable solvent vehicle to obtain a solution with a concentration of 5-60%, adding butylphthalide into the solution, stirring to obtain a liquid inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivatives. Claims 7-8 are drawn to said process further involving steps of drying, precipitation and filtering to produce specific forms of said complex, and the use of specific solvents. Claims 9-10 are drawn to a process of preparing said inclusion complex with cyclodextrin or cyclodextrin derivatives comprising specific steps involving drying, precipitation and filtering to produce specific forms of said complex, and the use of specific solvents.

Habon et al. disclose a method of complexation of drugs with cyclodextrin to enhances the bioavailability of said drugs in vivo (see abstract). Furthermore, Habon et al. disclose that the enhanced the bioavailability of drugs upon complexation are due factors such as enhanced dissolution rates and higher solubility (see abstract). In addition, Habon et al. disclose that the

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enhanced bioavailability is controlled or depends on factors such as solubilities, stability constants and the molar ratio of drug to cyclodextrin. Habon et al. disclose that the compounds can be administered in oral dosage forms (see abstract).

The difference between applicant's claimed method and the method of Habon et al. is the type of drug used.

Xu et al. disclose that butylphthalide has antithrombotic activity and antiplatelet activity when administered to rats (see abstract).

It would have been obvious to one having ordinary skill in the art at the time the claimed invention was made in view of Habon et al. and Xu et al. to use the method of Habon et al. to prepare a complex of butylphthalide with cyclodextrin or a derivative in order to enhance the bioavailability of drug due to complexation by administering said complex to a subject and consequently to improve the treatment of thrombosis.

One having ordinary skill in the art would have been motivated in view of Habon et al. and Xu et al. to use the method of Habon et al. to prepare a complex of butylphthalide with cyclodextrin or a derivative in order to enhance the bioavailability of drug due to complexation by administering said complex to a subject and consequently to improve the treatment of thrombosis, based on factors such as the severity of the thrombosis and the type of subject treated. It should be noted that the use of specific ratios of drug to cyclodextrins also depends on factors such as the severity of the thrombosis and the type of subject treated. It should be noted that the use of specific forms or formulations of said drugs such as butylphthalide is well-known in the art and is well within the purview of a skilled artisan. Also, the use of common solvents and conventional techniques such as drying, precipitation and filtration in order to purify or

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produce specific forms a compound such as butylphthalide is common in the well-known in the art and is well within the purview of a skilled artisan.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (Yaoxue Xuebao (1999), 34(3), 172-175) in view of Habon et al. (Pharmazie (1984), 39 (12), pages 830-4).

In claim 15, applicant claims a method of treating ischemia-induced disease comprising administering a therapeutically effective amount of the inclusion complex according to claim 1 to a patient.

Xu et al. disclose a method of treating cerebral ischemia by administering butylphthalide to rats (see abstract).

The difference between applicant's claimed method and the method of Xu et al. is that applicant's compound is complexed with cyclodextrin.

Habon et al. disclose that complexation of drugs with cyclodextrin enhances the bioavailability of drugs in vivo (see abstract). Furthermore, Habon et al. disclose that the enhanced bioavailability of drugs upon complexation are due factors such as enhanced dissolution rates and higher solubility (see abstract). In addition, Habon et al. disclose that the enhanced bioavailability is controlled or depends on factors such as solubilities, stability constants and the molar ratio of drug to cyclodextrin. Habon et al. disclose that the compounds can be administered in oral dosage forms (see abstract).

It would have been obvious to one having ordinary skill in the art at the time the claimed invention was made in view of Xu et al. and Habon et al. to use the method of Xu et al. to treat ischemia such as ischemia-induced disease in a subject by administering a complex of

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butylphthalide with cyclodextrin or a derivative to said subject in order to enhance the bioavailability of the drug due to complexation and consequently to improve the treatment of thrombosis.

One having ordinary skill in the art would have been motivated in view of Xu et al. and Habon et al. to use the method of Xu et al. to treat ischemia such as ischemia-induced disease in a subject by administering a complex of butylphthalide with cyclodextrin or a derivative to said subject in order to enhance the bioavailability of the drug due to complexation and consequently to improve the treatment of thrombosis, based on factors such as the severity of the thrombosis and the type of subject treated. It should be noted that the use of specific ratios of drug to cyclodextrins also depends on factors such as the severity of the thrombosis and the type of subject treated.

Response to Arguments

Applicant's arguments with respect to claims 11-18, 21-27, 34-47 have been considered but are not found convincing.

The applicant argues that one skilled in the art would understand from Xu2001 that butylphthalide is only sometimes effective, but is effective when administered as essentially pure active agent. Consequently however, one skilled in the art would expect a lower ratio or percent of the active agent would be required when said active agent is complex with the cyclodextrin since the cyclodextrin enhances the bioavailability of the drug due to complexation. That is, one having ordinary skill in the art would have been motivated in view of Xu et al. and Habon et al. to have prepared a complex of butylphthalide with cyclodextrin or a derivative in order to enhance the bioavailability of the drug due to complexation by administering said complex to a subject

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and consequently to improve the treatment of thrombosis, based on factors such as the severity of the thrombosis and the type of subject treated.

The applicant argues that Habon is theoretical and completely ignores the fact that it would be impossible for all drugs with different molecular structures, sizes or molecular weights in properties to be successfully complexed with cyclodextrin to improve solubilities or any other characteristics. Moreover, it must be remembered that the Applicants maintain the molar ratio, of butylphthalide to cyclodextrin at a ratio of 1:1-10. In other words, the active agent is at most at about a 50% ratio relative to the cyclodextrin. This is sharply contrasted to the Xu 2001 disclosure which employs substantially pure butylphthalide. Given that Xu 2001 established that it was in many instances unsuccessful in showing activity, but in any event showed successful activity at near pure levels, the Applicants respectfully submit that one skilled in the art would not reasonably expect an inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivatives at a molar ratio of no more that about 50% butylphthalide to be effective. In fact, the Applicants respectfully submit that one skilled in the art would have a reasonable expectation that it would not be successful because of the prior demonstration by Xu 2001 that nearly pure butylphthalide is needed to have some expectation of Success. On the contrary however, one skilled in the art would expect a lower ratio or percent of the active agent would be required when said active agent is complex with the cyclodextrin since the cyclodextrin enhances the bioavailability of the drug due to complexation. Consequently, one having ordinary skill in the art would have been motivated in view of Xu et al. and Habon et al. to have prepared a complex of butylphthalide with cyclodextrin or a derivative in order to enhance the bioavailability of the drug due to complexation by administering said complex to a subject and consequently to

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improve the treatment of thrombosis, based on factors such as the severity of the thrombosis and the type of subject treated.

The applicant argues that Xu 2001 does not disclose cyclodextrin and, accordingly; inherently does not disclose the first step of adding cyclodextrin or cyclodextrin derivatives into a solvent to obtain a solution with a concentration of 5-60%. However, Habon et al. discloses the use of cyclodextrin as set forth above and the rejection was made over Habon et al. in view of Xu et al. (see above rejection).

The applicant argues that there is: also no disclosure of the Applicants' claimed subject matter, of adding cyclodextrin or cyclodextrin derivatives into a solvent to obtain a solution with a concentration of 50-60%. This is also important because it means that the hypothetical combination of Xu 2001 with Habon would still result in a process for preparing a complex that does not include the step of adding cyclodextrin or cyclodextrin derivatives into a solvent vehicle to obtain a solution of a concentration of 5-60%. However, it should be noted that the complexation of a drug such as butylphthalide by addition or mixing of the commonly used complexing agent cyclodextrins to said drug is well-known in the art and is well within the purview of a skilled artisan. Also, the order in which the butylphthalide and the cyclodextrin are mixed or are added to each other should not affect the complex produced. Furthermore, it should be noted that applicant has not indicated that said order affects the complex produced.

The applicant argues that Habon completely ignores the concentration of cyclodextrin or cyclodextrin derivatives in the Solvent. There is no disclosure on this point at all. There is some minor disclosure of the molar ratios of a drug (although none are specifically identified) to cyclodextrin, there is no mention of the cyclodextrin concentration relative to the solvent. For

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example, there is a drug/cyclodextrin molar ratio of 1:1 on page 831, right-hand column, mid paragraph, and a drug to cyclodextrin molar ratio of 1:2 on the same page at the bottom of the paragraph. However, there is no disclosure of the concentration of cyclodextrin or cyclodextrin derivatives with respect to the solvent. However, it should be noted that the use of specific ratios of drug to cyclodextrins also depends on factors such as the severity of the thrombosis and the type of subject treated.

The applicant argues that importantly, there is also a disclosure in Xu 1999 that nearly pure 3-n-butylphthalide with a purity of more, than 96% was used. Thus, like Xu 2001, one skilled in the art would not have reasonable expectation of success that the combination of Habon with Xu 1999 would result in a Successful method of treating ischemia-induced disease. The reason is that Xu1999 uses nearly pure butylphthalide and the Applicants' Claim 15 uses an inclusion complex wherein, the molar ratio butylphthalide to cyclodextrin or cyclodextrin derivatives is at most about 50% butylphthalide. As a result, one skilled in the art would have no expectation with respect to utilization of the claimed inclusion complex in a method of treating an ischemia-induced disease. Consequently however, one skilled in the art would expect a lower ratio or percent of the active agent would be required when said active agent is complex with the cyclodextrin since the cyclodextrin enhances the bioavailability of the drug due to complexation. That is, one having ordinary skill in the art would have been motivated in view of Xu et al. and Habon et al. to have prepared a complex of butylphthalide with cyclodextrin or a derivative in order to enhance the bioavailability of the drug due to complexation by administering said complex to a subject and consequently to improve the treatment of

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thrombosis, based on factors such as the severity of the thrombosis and the type of subject treated.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Henry whose telephone number is 571-272-0652. The examiner can normally be reached on 8.30am-5pm; Mon-Fri. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Michael C. Henry

April 27, 2008.

/Shaojia Anna Jiang, Ph.D./

Supervisory Patent Examiner, Art Unit 1623